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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/567,872	05/19/2006	Ilia Fishbein	RCHP-135US	1203

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EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	PAPER NUMBER
1632	
MAIL DATE	DELIVERY MODE
09/08/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/567,872	FISHBEIN ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,8-10,17-28 and 35-37* is/are pending in the application.

4a) Of the above claim(s) *17-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,8-10 and 35-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 February 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim amendments filed on 07/01/2010 have been received and entered.

Claims 2, 4-7, 11-16, 29-34, and 38-40 are cancelled. Claims 1, 3, 8-10, 17-28, and 35-37 are pending. Claims 1, 17-19, 21, 22, 36, and 37 have been amended.

Claims 17-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim.

Claims 1, 3, 8-10, and 35-37 are currently under examination.

This application 10/567,872 is a 371 of PCT/US04/26509 filed on 08/13/2004, which claims benefit of 60/494,886 filed on 08/13/2003.

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

1. Previous rejection of claim 37 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is ***withdrawn*** because the claim has been amended.

Amended claim 37 has been amended to read as follows: The composition of claim 35, wherein the modified protein further comprises a receptor targeting ligand selected from the group consisting of apolipoprotein E, transferring, a vascular endothelial growth factor, a transforming growth factor-beta, a fibroblast growth factor, an RGD containing peptide, and folic acid.

Amended claim 37 no longer recites "the receptor targeting ligand".

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1, 3, 8-10, and 35-37 remain rejected under 35 U.S.C. 103(a) as being unpatentable over **Levy et al.** (U.S. 2003/0044408, publication date, 03/06/2003, filed on 06/14/2000; this reference is cited in the IDS filed by Applicant on 08/20/2008) in view of **Li** (US patent 6,524,572, issued date 02/25/2003, filed on 09/26/2000). Applicant's arguments filed 07/01/2010 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 3-10 of the office action mailed on 02/19/2010 and is reiterated below with revisions addressing claim amendments filed on 07/01/2010.

Amended claim 1 filed on 07/01/2010 reads as follows: A composition comprising a metal surface chemically coordinated to a surface modifier, a gene transfer vector, and a modified protein, wherein the modified protein comprises a CAR protein or a fragment of a CAR protein, the gene transfer vector is bound to the CAR protein or the fragment of the CAR protein, and the modified protein is covalently bound to the surface modifier directly or via a linker.

Claim 3 further limits claim 1 by the limitation wherein the modified protein is covalently bound to the surface modifier through a thio residue and a linker.

Claim 8 further limits the metal surface being a surface of a medical device.

Claim 9 further limits claim 8 to medical device selected from the group consisting of a stent, a heart valve, a wire suture, a joint replacement, a urinary dilator, an orthopedic dilator, a catheter and an endotracheal tube.

Claim 10 further limits claim 8 to the medical device being at least one of an internal device and an external device.

Claim 35 further limits claim 1 by the limitation wherein the modified protein comprises a fragment of a CAR protein.

Claim 36 further limits claim 35 by the limitation wherein the fragment of the CAR protein is an extracellular domain of the CAR protein or an immunoglobulin D1 domain of the CAR protein.

Claim 37 further limits claim 35 by the limitation wherein the modified protein further comprises a receptor targeting ligand is selected from the group consisting of apolipoprotein E, transferrin, a vascular endothelial growth factor, a transforming growth factor-beta, a fibroblast growth factor, an RGD containing peptide, and folic acid.

Claim interpretations: **(i)** The limitation "wherein the modified protein comprises a CAR protein or a fragment of a CAR protein" recited in claim 1 encompasses the modified protein is a fusion protein. This interpretation is consistent with the word "comprising", which allows the presence of non-specified sequences, and is consistent with the limitation of claim. **(ii)** The limitation "gene transfer vector" recited in claim 1 refers to all vectors with which one or more therapeutic genes can be transferred or introduced into the desired target cells and, in particular, viral vectors having this property. In the majority of cases of gene therapy, a viral vector is used to introduce the gene to be expressed into appropriate cells. This interpretation is based on the disclosure provided in instant application (See paragraph [0009], US 2007/0092489, publication date 04/26/2007).

With regard to limitations of claims 1, 8, and 10, **Levy et al.** teaches a composition comprising a surface modifier and a metal support to which said surface modifier is chemically coordinated. Preferably, the surface modifier is an aminobisphosphonate. Levy et al. teaches

that, still preferred, the surface modifier is a polyamine, and in another aspect of the invention, the composition further comprises a biologically active molecule. Levy et al. teaches that in another preferred embodiment, the biologically active molecule is an antibody which specifically binds a nucleic acid; and also preferred the nucleic acid comprises a vector system. Levy et al. teaches that in yet another aspect of the invention, the biologically active molecule is preferably one component of an affinity pairing system, and still preferred, the biologically active molecule is avidin or biotin; IgG or protein A; or transferrin or its receptor (See paragraph [0008], Levy et al., 2003/0044408, 2003). Levy teaches that a therapeutic delivery system efficiently introduces biologically active molecules to mammalian cells without the use of synthetic polymers or biopolymer coatings. Levy teaches that surface modification of a metal support, such as stainless steel and titanium medical devices, a stainless steel stent, results in a single molecular layer that can fasten various molecules, thereby minimizing any cellular inflammatory response while enhancing biocompatibility (See abstract, and paragraph [0003] and [0010] Levy et al., 2003). Levy et al. teaches that the paired component which is most suitable for attachment to the surface-modified metal would be immobilized. The component is covalently cross-linked to a monomeric or polymeric surface modifier, which, in turn, provides chemical moieties that bind to the metal surface (See abstract, and paragraph [0026] and [0037], Levy et al., 2003).

With regard to the limitation "wherein the modified protein is covalently bound to the surface modifier through thiol residue and a linker" recited in claim 3, Levy teaches that in Fig. 2 depicts a reaction scheme for modifying surfaces of metal supports via amino group containing bisphosphonates. During an activation step, the N-succinimidyl ester group in SPDP (N-succinimidyl-3-(2-pyridyl- dithio)-propionate) reacts with the amino group of a chemosorbed

polyamino-bisphosphonic acid, to activate a steel surface with a pyridyldithio group, and during a modification step, a thiol modified antibody is chemically linked to the metal (See paragraph [0013], US 2003/0044408. Levy et al, 2003).

With regard to the limitation of medical devices recited in claim 9 and the limitation of internal device and external device recited in claim 10, Levy et al. teaches that medical devices may include non-orthopedic devices, temporary placements and permanent implants, such as tracheostomy devices, intraurethral and other genitourinary implants, stylets, dilators, stents, vascular clips and filters, pacemakers [which reads on internal device], wire guides and access ports of subcutaneously implanted vascular catheters [which reads on external device]. (See paragraph [0036], US 2003/0044408. Levy et al, 2003).

Related to the limitation "wherein the modified protein comprises a fusion protein, or a CAR (coxsackievirus/adenovirus receptor) protein or a fragment of a CAR protein" recited in claim 1, the limitation "wherein the modified protein is comprises fragment of a CAR protein" recited in claim 35, the extracellular domain of CAR or an immunoglobulin D1 domain of CAR recited in claim 36, and the receptor targeting ligand recited in claim 37, Levy et al. teaches the composition comprises a biologically active molecule. Levy et al. teaches that the biologically active molecule is preferably one component of an affinity pairing system, and still preferred, the biologically active molecule is avidin or biotin; IgG or protein A; or transferrin or its receptor (See paragraph [0008], US 2003/0044408. Levy et al, 2003).

Levy et al. does not explicitly teach the limitation "wherein the modified protein comprises a CAR protein, or a fragment of a CAR protein" recited in claim 1, the limitation "wherein the modified protein comprises fragment of a CAR protein and a receptor targeting

ligand" recited in claim 35, the fragment/domain of the CAR protein recited in claim 36, and the receptor targeting ligand recited in claim 37.

Li teaches recombinant virus with a bispecific fusion protein ligand in coupling with an antibody to cell for gene therapy, and the fusion protein comprises extracellular domain of CAR/Hinge/protein A ligand, and Li develops a strategy using adenovirus as an example to demonstrate the strategy of using the fusion protein to re-direct viral tropism (See title, abstract and Figure 1, Li). Li teaches that any extracellular domain of a viral receptor that is a membrane protein or membrane peptide can be used to replace extracellular domain of CAR (coxsackievirus/adenovirus receptor) and can be inserted as a part of the fusion protein ligand for targeting (See lines 20-24, column 8, Li). Li further teaches that Arg-Gly-Asp (RGD) motif of viral pentose protein binds to integrins of cell membrane and this binding activates virus internalization via receptor-mediated endocytosis (lines 53-58, column 1, Li). It is noted that the recombinant adenoviral vector used for delivery of therapeutic gene for gene therapy purpose taught by Li et al. is clearly encompassed by the amended limitation "gene transfer vector" recited in claim 1.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Levy et al. regarding a composition comprising a surface modifier and a metal support to which said surface modifier is chemically coordinated, and the composition further comprises a biologically active molecule, the biologically active molecule being an antibody, and also preferred, the biologically active molecule being preferably one component of an affinity pairing system, and still preferred, the biologically active molecule is avidin or biotin; IgG or protein A; or transferrin or its receptor,

with the teaching of Li regarding fusion protein comprises extracellular domain of CAR/receptor targeting ligand, to arrive at the claimed invention of claims 1, 3, 8-10, and 35-37.

One having ordinary skill in the art would have been motivated to combine the teachings of Levy et al. and Li et al. because the fusion protein taught by Li can target specifically the receptor of interest present on cell membrane in the context of using viral vector for gene therapy to deliver therapeutic gene via the metal surface of a medical device, for instance, a stent taught by Levy et al.

There would have been a reasonable expectation of success given (i) successful demonstration of a composition comprising a surface modifier and a metal support to which said surface modifier is chemically coordinated, and the composition further comprises a biologically active molecule, and virus tethering stainless steel and in vivo cell transduction (See Example 5 of Levy et al.), by the teachings of Levy et al., and (ii) successful construction of vector expressing the fusion protein comprises extracellular domain of CAR/receptor targeting ligand (See lines 20-24, column 8, and lines 53-58, column 1 of Li), and a recombinant adenoviral vector bound to the CAR protein (See Figure 1 of Li), by the teachings of Li.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's arguments

Applicant argues that Levy and Li do not teach or suggest all the limitations in the proposed amended claim 1. As conceded by the Examiner, Levy does not teach a CAR protein or a fragment thereof. Applicant states that while Li teaches binding of a recombinant virus to a CAR protein, Li fails to teach binding of nucleic acid, for example, a gene transfer vector, to a CAR protein or a fragment thereof. Applicant states that in view of Levy and Li, one of ordinary skill in the art would not have been motivated to combine a metal surface, a CAR protein or a

fragment of a CAR protein, and a gene transfer vector with a reasonable expectation of success in immobilizing the gene transfer vector to the surface via the CAR protein or the fragment thereof. Applicant concludes that the amended claim 1 and its dependent claims are not obvious over Levy and Li.

Response to Applicant's arguments

It is noted that the amended claim 1 file don 07/01/2010 does not require "binding of nucleic acid to a CAR protein or a fragment thereof" as Applicant argues. It is worth noting that a direct "binding of nucleic acid to a CAR protein or fragment thereof" would generate a peptide nucleic acid (PNA), and the specification of instant application does not disclose any information pertaining to peptide nucleic acids (PNAs). On the other hand, Applicant does acknowledge and agree that Li teach "binding of a recombinant virus to a CAR protein", which reads on the limitation "the gene transfer vector is bound to the CAR protein or the fragment of the CAR protein" as recited in amended claim 1 filed on 07/01/2010. Furthermore, as stated in the maintained rejection, the limitation "gene transfer vector" recited in claim 1 refers to all vectors with which one or more therapeutic genes can be transferred or introduced into the desired target cells and, in particular, viral vectors having this property. In the majority of cases of gene therapy, a viral vector is used to introduce the gene to be expressed into appropriate cells. This interpretation of "gene transfer vector" is based on the disclosure provided in instant application (See paragraph [0009], US 2007/0092489, publication date 04/26/2007). Therefore, the recombinant adenoviral vector used for delivery of therapeutic gene for gene therapy purpose taught by Li clearly encompassed by the amended limitation "gene transfer vector" recited in claim 1.

Conclusion

3. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

4. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Wu-Cheng Winston Shen/
Primary Examiner
Art Unit 1632